REMARKS

As noted above, the claims are amended to delete certain sequences in order to expedite grant. In particular Claims 43, 44, 45, have been amended to delete reference to SEQ ID NO:13, 15, 17, and 17. These amendments should render moot the outstanding rejections and objections.

Turning to the Office Action Claim 50 stands objected to as allegedly being of improper dependent form. The basis of the objection is the Examiner's position that it is unclear that SEQ ID NO:13 is present in SEQ ID NO:10 and 11. With respect thereto in the present Office Action she questions the relationship between these sequences with particular reference to Figure 9. She also questions the absence of alignment data showing the relationship of these sequences.

Claim 50 is presently cancelled. Therefore, the objection to this Claim is not applicable.

In addition, while moot the objection to cancelled Claim 50 is moot, it is unsustainable in view of the fact that the specification clearly and thoroughly teaches that that the subject matter of the inventions concerns the correlation of gene expression (determined at the level of transcription by detecting transcript) with a specific disease (a subtype of B-CLL). By demonstrating that the primary transcript (SEQ ID NO: 11) correlates with the disease (in the Northern Blot of Figure 3 in the present application) it follows that further transcript processed from the primary transcript (e.g. by splicing of RNA) also will follow the disease. The experimental data submitted with the application confirms the claimed correlation by employing different means of methods and probes for detection. The inventors have further substantiated the above claimed correlation between CLLU-1 expression and the subtype of B-CLL in several published studies. Finally and most importantly, the method of the invention has been implemented in the clinic.

Taken together, the core of the present invention is very simple – transcription of the CLLU-1 gene (identified by the Applicant) correlates with a subtype of B-CLL. This fact is clearly stated in the specification (page 8, lines 6-17), which teaches that the present invention is based on the discovery that an expression product, which comprises at least one nucleotide sequence selected from the group consisting of SEQ NO 12 to 18 (the sub-sequences), correlates with the subtype of B-CLL. Since the statement refers to expression product comprising a nucleotide sequences, it follows that the expression product is <u>not</u> a translation product (protein). It also follows that the cited nucleotide sequence is <u>not</u> a DNA product because DNA matter is <u>not</u> a gene expression

product. The specification does not leave the skilled person in any doubt that the subject matter of the present invention relates to detecting transcripts of CLLU-1, which correlates with the subtype of B-CLL.

The objection under II appears to be based on the sole fact that the subsequences SEQ NO 12 to 18 have erroneously been annotated in the sequence listing as DNA. As explained in the previous response, it is normal practice to submit a sequence of transcripts to gene banks in the DNA format although the matter concerns a newly identified transcript. Faced with a sequence in the DNA format, the skilled person would still acknowledge the sequence as valid representation of the corresponding RNA sequence. He would not even bother replacing the T with U before making use of the information provided with the sequence. Thus, it seems beyond reason that the Examiner object the subject matter relating to the detection of at least one transcription product, wherein said at least one transcription product comprises a RNA nucleotide sequence selected from the group consisting of subsequences identified by the SEQ NOs 12 to 18, for the reason these have been erroneously annotated DNA in the sequence listing. In particular in view of the fact that the specification clearly teaches that mRNA sequences comprising a least one of the subsequences have been found patients with the specific subtype of B-CLL (e.g. page 10, lines, 4-9).

Claims 43-48 and 50-57 also stand rejected under 35 USC 112 first paragraph as failing to comply with the written description requirement of the statute. Essentially, the Examiner's concern seems to be her position that the specification refers to a "transcribed sequence of the cDNA sequence set forth in" SEQ ID NO: 13, 15, 16 and 17, allegedly introducing new matter into the claims. Also she suggests that SEQ ID NO:13, 15 and 16 are identified as exons and that SEQ ID NO:17 as a coding sequence and that "there is no indication that these sequences are cDNAs as they are not labelled as such.

In response thereto it is noted that these sequences are no longer referred to in any of the pending claims as a result of the present amendments of claims 43, 44 and 45. Therfore, the rejection should be moot. Accordingly withdrawal of this written description rejection of Claims 43-48, and 50-57 under 35 USC 112 first paragraph is respectfully requested.

In addition, while moot this rejection is also unsustainable. The written description rejection of these claims appears to be based on the sole fact that the subsequences SEQ NO 12 to 18 have erroneously been annotated in the sequence listing as DNA. As explained in the previous response, it is normal practice to submit a sequence of transcripts to gene banks in the DNA format although the matter concerns a newly identified transcript. Faced with a sequence in the DNA format, the skilled person would still acknowledge the sequence as valid representation of the corresponding RNA sequence. He would not even bother replacing the T with U before making use of the information provided with the sequence. Thus, it seems beyond reason that the Examiner object the subject matter relating to the detection of at least one transcription product, wherein said at least one transcription product comprises a RNA nucleotide sequence selected from the group consisting of subsequences identified by the SEQ NOs 12 to 18, for the reason these have been erroneously annotated DNA in the sequence listing. In particular in view of the fact that the specification clearly teaches that mRNA sequences comprising a least one of the subsequences have been found patients with the specific subtype of B-CLL (e.g. page 10, lines, 4-9).

In any event, the rejection is now moot based on the present amendments of claims 43, 44 and 45 deleting the reference to SEQ ID NO: 13, 15, 16 and 17.

Claims 43-48, 50-57 and 61-66 also stand rejected under 35 USC 112 first paragraph as failing to comply with the enablement requirement of the statute. Again based on Applicant's understanding of the rejection the Examiner's concern would seem to be her position that the specification does not enable assays for detecting specific RNA transcripts because the sequences in SEQ ID NO: 13 and 15-17 are cDNA's . Again, it is anticipated that this rejection should be moot as the claims no longer refer to these sequences. Accordingly withdrawal of this rejection of Claims 43-48, 50-57 and 61-66 under 35 USC 112 first paragraph is respectfully requested.

This is assertedly because in the sequence listing SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17 are designated as DNA sequences. The Examiner concludes that the application does not enable a method for establishing a diagnosis of a subtype of B-CLL by

detecting the presence of DNA comprising a sequences set forth in one of SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17.

The Examiner considers that the application does not provide enablement for detecting a transcript, which essentially is defined by one of the sequences set forth in the sub-sequences (SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17).

Again while the rejection is now moot it also is unsustainable. It is conceded that the previously recited subsequences (now deleted) are not necessarily present as mature spliced transcripts as such, in the sense of a transcript originating from the splicing process of the primary transcript, i.e., they may be present in the form of rare degradation products. However, it follows that if the primary transcripts and the spliced products derived thereof correlate with the subtype of B-CLL, that the products identified as specific degradation products of the former will correlate to the disease as well.

The purpose of the enablement requirement that the specification describe the invention in such terms that the one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way (MPEP paragraph 2164). The Applicant sincerely believes that the skilled person would acknowledge that even if the subsequences identified by the SEQ NOs 13, 15, 16 and 17 are only sparsely present in the form of RNA, that their presence could be detected as claimed and would correlate with the subtype of B-CLL in view of the fact that they originate from transcripts of CLLU-1. For the clinical application of the method of invention, person skilled in the art would obviously prefer assessing the diagnose/prognose by detecting abundant transcripts of CLLU-1.

However, again in the sole purpose of expediting the prosecution of the present application the Applicant submits an amended set of claims no longer reciting the subsequence SEQ NOs 13, 15, 16 and 17. The amended claims are now limited to the detection of RNA transcripts comprising the sequences set forth in SEQ ID NOs 2, 4, 6, 7, 10, and 11. It is further noted that after Applicant's response dated May 5, 2009 the Examiner noted that she was willing accept claims directed towards the transcripts identified in the present application by the SEQ ID NOs 2, 4, 6, 7, 10, and 11. Accordingly, the claims should be in condition for allowance.

In addition, while not germane to the written description or enablement of any pending claim, in response to questions raise by the Examiner concerning Figure 9, Applicants further provide clarification and supporting data (alignments) concerning the structural relationship between the previously recited and presently claimed transcripts. Applicants acknowledge that Figure 9 does not very well illustrate the structural relationship between the recited CLLU-1 transcripts.

In particular Applicant therefore submits alignments of the following transcripts:

SEQ ID NO: 11 (the primary transcripts) and the subsequences SEQ NOs 13, 15, 16 and 17 against SEQ NO: 1 (genomic BAC clone) are aligned in **Exhibit A**. The alignment clearly shows that the primary transcripts (SEQ ID NO: 11) originates from the CLLU-1 gene located in the genomic sequences of SEQ NO: 1. The alignment further shows that the subsequences perfectly aligns to the primary transcripts thus confirming that these that the primary transcripts (SEQ ID NO: 11) comprises all of the subsequences SEQ ID NOs 13, 15, 16 and 17 as previously claimed. Thus, the alignment provided in **Exhibit A** confirms that the SEQ ID NO: 11 (the primary transcripts) originates from the genomic DNA of the CLLU-1 gene and that the transcript comprises all of the subsequences SEQ NOs 13, 15, 16 and 17.

SEQ ID NO: 2 (transcript) against SEQ ID NO: 11 (the primary transcripts) and the subsequences SEQ ID NOs 13, 15, 16 and 17 are aligned in **Exhibit B**. The alignment shows that SEQ ID NO: 2 originates from SEQ ID NO: 11 and also comprises the subsequences SEQ ID NOs 15, 16 and 17.

SEQ ID NO: 4 (transcript) against SEQ ID NO: 11 (the primary transcripts) and the subsequences SEQ ID NOs 13, 15, 16 and 17 are aligned in **Exhibit C**. The alignment shows that SEQ ID NO: 4 originates from SEQ ID NO: 11 and also comprises the subsequences SEQ ID NOs 13 (partly), 15, 16 and 17.

SEQ ID NO: 6 (transcript) against the subsequences SEQ ID NOs 13 and 16 are aligned in **Exhibit D**. The alignment shows that SEQ ID NO: 6 contains SEQ ID NOs 13 and 16, which are subsequences of SEQ ID NO: 11 and thus confirms that SEQ ID NO: 6 originates from SEQ ID NO: 11.

SEQ ID NO: 7 (transcript) against the subsequences SEQ ID NOs 13 and 16 are aligned in **Exhibit E**. The alignment shows that SEQ ID NO: 6 contains SEQ ID NOs 13, 15 and 16, which are subsequences of SEQ ID NO: 11 and thus confirms that SEQ ID NO: 7 originates from SEQ ID NO: 11.

Finally, SEQ ID NO: 10 (transcript) against SEQ ID NO: 11 (the primary transcripts) and the subsequences SEQ ID NOs 13, 15, 16 and 17 are aligned in **Exhibit F**. The alignment shows that SEQ ID NO: 7 originates from SEQ ID NO: 11 and also comprises the subsequences SEQ ID NOs 15, 16 and 17.

Taken together, the submitted sequence alignments (**Exhibit A to F**) confirm that the primary CLLU-1 transcript (SEQ ID NO: 11) is a transcripts of the genomic region encoding the CLLU-1 gene (SEQ ID NO:1) and the transcripts comprises all of the subsequences identified by the sequences set forth in SEQ ID NOs 13, 15, 16 and 17. Further the alignments confirm that the transcripts identified by the sequences set forth in SEQ ID NOs 2, 4, 6, 7, and 10 originates from the sequence set forth in SEQ ID NO: 11 by comprising at least one of the subsequences. Thus, the submitted sequence alignments confirm that the sequences cited in the claims are structurally related and originating from the same gene and derived from the primary transcripts set forth in the sequences identified by SEQ ID NO: 11 (demonstrated by the considerable overlapping sequences). The Applicant therefore respectfully submits that the question concerning the structural relationship between the sequences cited in the claims have been more than sufficiently addressed.

Based on the foregoing amendments and remarks it is anticipated that the present amendments will place this case in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding the Examiner is requested to contact the undersigned.

The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. § 1.16 and § 1.17 associated with this communication or credit any overpayment to the deposit account of Hunton & Williams, **Deposit Account Number 50-0206.**

Respectfully submitted,

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Dated: July 14, 2010 By: _____

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